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ORIGINAL PAPER

# Mortality of 403 patients with mood disorders 48 to 52 years after their psychiatric hospitalisation

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**Abstract** The purpose is to analyse differences in mortality among patients with major depressive disorders (MDD), bipolar-II (BP-II), bipolar-I (BP-I) disorders and mania with or without minor depressive disorders and to identify risk factors of mortality. The sample represents all admissions for depression or mania over 5 years (1959–1963) to the Psychiatric Hospital of Zurich University, serving a large area. 403 patients were included and followed up every 5 years until 1985; thereafter, mortality data were collected repeatedly until 2009 when 352 (87 %) patients had died. Standardised mortality ratios (SMRs) were computed and survival analyses applied. With the exception of BP-II disorder, the three other diagnostic groups showed elevated SMRs. The group with mania had the highest SMR for cardiovascular deaths and the group with MDD the highest for deaths by suicide. Mortality was also high among patients with late-onset MDD. Across the diagnostic spectrum, we found differences in risk factors for mortality, such as a family history of suicides and personality type: more anxious patients with MDD lived longer, and among patients with BP disorders, more tense (aggressive) types had shorter lives. Long-term medication had a protective effect against mortality in patients with MDD during years 1–9 and in patients with BP disorders during years 1–19 after admission. We found marked differences in causes of death and risk factors between subgroups of mood disorders. For the purpose of further research, it would be recommendable to distinguish pure mania from bipolar disorders.

**Keywords** Mortality · Mania · Depression · Bipolar disorders · Risk factors · Suicide · Personality

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## Introduction

Mood disorders are the most common psychiatric disorders, with lifetime prevalence rates between 20 and 30 % or higher in the general population. The WHO ranks the burden of depression second among all medical disorders, after cardiovascular diseases [1, 2].

Elevated mortality is an important aspect of the Global Burden of Disease. It is generally assumed that depressed patients have a shorter life expectancy, although a review of the literature by Cole [3] raised some doubts in this regard. Nonetheless, a number of the studies covered by the review provide evidence that mortality is higher among depressed patients even after adjustment for demographic and medical risk factors [4] or disability [5]. In addition, several sound prospective studies have demonstrated increased mortality among elderly depressed patients [5–12]. This was especially so for deaths by suicide within the first 12 months of contact with the public mental health service of England and Wales from 1996 to 2000 ($N = 4{,}859$); risk factors were living alone, recent bereavement and physical illness [13].

The largest representative studies of the mortality of patients admitted to psychiatric hospitals are those based on population registers in Sweden and Denmark. In Sweden, the standardised mortality ratios (SMRs) for death

by suicide for 15,386 patients admitted to hospital for bipolar disorder (BP) and 39,182 admitted for unipolar disorders (UP) between 1973 and 1995 were 15.0 for men with BP and 22.4 for women with BP, and 20.9 for men with UP and 27.0 for women with UP [14]. Natural deaths accounted for about half of the total mortality; the SMR decreased with age. A Danish study confirmed a very high risk of death by suicide among 54,103 patients with affective disorders during the first 12 months following their first admission compared to later years [15]. The largest such study, by Munk Laursen et al. [16] in Denmark, compared 105,841 of 261,886 patients admitted to a psychiatric hospital who had died with the population of 1,480,608 persons without psychiatric hospitalisation who had died (years 1973–2001). Patients with unipolar depressive disorder, bipolar disorder and schizoaffective disorder had similar patterns of excess mortality. Among patients hospitalised for mood disorders, mortality rate ratios for suicide were much higher for women (UP 37.2 and BP 43.2) than for men (UP 25.9 and BP 24.0). Deaths by homicide were also higher among women but deaths by accident were higher among men with UP and BP. The most recent studies suggest that the mortality rate among patients with bipolar disorder is strongly elevated [17, 18] and is higher among patients with bipolar-I (BP-I) disorder than among those with bipolar-II (BP-II) disorder [16].

Prospective cohort studies of hospitalised patients conducted over decades are both very rare and small in their sample sizes but they can add to our understanding of further correlates of mortality and the differences between diagnostic subgroups of mood disorders. To our knowledge, there are no studies on mortality lasting more than 40 years. The present update can contribute to filling that gap.

The initial purpose of our 50-year-long prospective cohort study was to describe the course and outcome of mood disorders [19, 20]; subsequently, it aimed at determining (1) the mortality risk of subjects with severe affective disorders, considering subgroups across the mood spectrum from depression via bipolar subgroups to mania, and comparing it to the mortality risk of the general population and (2) to identify the factors which were associated with mortality. In 2002, we presented the results of a follow-up period of 34–38 years [21]; a second report focussed especially on 45 suicides up to 2003 [22]. This third paper covers a further 6 years up to 2009.

## Methods

### Patient sample

The sample of the present study consists of 406 patients, representing all admissions to the Psychiatric Hospital of Zurich University for major mood disorders between 1959 and 1963. Originally, that is, until 1985, the purpose of the clinical follow-up was to describe the course and outcome of the disorders [19, 20]. By nature, it later developed into a study on mortality. When the *final clinical diagnosis* was made in 1985, all 406 subjects met DSM-IV criteria of major depressive or manic episodes and ICD-10 diagnoses for major mood disorders, and comprised 186 patients with UP and 220 patients with BP disorders. The latter group is subdivided into patients with BP-I ($N = 130$), patients with BP-II ($N = 60$) and patients with mania with or without minor depressive disorders ($N = 30$). Three (0.7 %) of the originally 406 patients could not be followed up because they had moved abroad. They all belonged to the subgroup of patients with UP, reduced thereby to 183 cases. All analyses were restricted to the remaining 403 subjects. Further methodological details were provided in earlier papers [19, 21].

### Semi-quantitative measures

The degree of remission during intervals was estimated by the Global Assessment Schedule (GAS) of Endicott et al. [23]. Information on personality was classified by Klesse and Zuberbühler on the basis of extensive psychiatric records and without knowledge of the final diagnosis made in 1985 [24, 25]. This assessment method was developed by Pössl and von Zerssen and by von Zerssen [26–28]. The personality variables were processed at the Max Planck Institute of Psychiatry in Munich by von Zerssen. They provide scores for six personality types: 'melancholic' according to Tellenbach [29, 30], 'relaxed, easy-going', 'manic', 'nervous, tense', 'unrealistic, dreamy' and 'anxious, insecure'.

### Data on mortality

After approval of the application by an ethical committee, the data on causes of death were provided by the Federal Office of Statistics of Switzerland.

### Statistical analysis

Expected deaths in the entire Swiss population were specifically determined for each of the following strata: gender (m/f), 5-year age intervals, each observation year (1959–2009), and each cause of death (grouped according to diagnostic entities). The standardised mortality ratio (SMR) was then determined by the sum of observed deaths in the patient sample divided by the sum of expected deaths in the Swiss population, each across all strata [31]. A SMR >1.0 reflects a higher risk of dying for the patients when compared to that risk in the Swiss population.

Chi-squared tests were used on frequency data and Kruskal–Wallis tests for continuous variables. SMRs were compared to population values and among patient groups by $t$ tests because SMRs are Poisson-distributed, and therefore, if $N$ is large, normally distributed.

To examine risk factors of all-cause mortality, we conducted a series of Cox proportional hazard models and extended Cox regression models with time-dependent covariates when necessary. The number of remaining years from admission until death was entered as the time-to-event variable. For time-dependent covariates, we estimated constant hazard ratios (HR) for different time intervals using Heaviside step functions [32]. Time-dependent hazard ratios were estimated separately for the intervals 1–9 years, 10–19 years, 20–29 years, 30–39 years, and 40 years and more (years refer to time after admission). Initial predictors were sex, long-term medication, number of medications, family history of suicide, psychotic symptoms, alcohol abuse, any substance abuse, presence of a broken home, social class, social deviation in personality, intelligence, percentage of time spent in illness, GAS score during interval, and the above-mentioned six personality types. Initial predictors were first all tested separately against mortality rates. Variables that yielded a significant model fit according to the likelihood-ratio $\chi^2$ test were included in a final multiple regression analysis. Variable exclusion relied on a backward stepwise method.

Analyses were carried out in SPSS 20 for Macintosh and Stata 11.2 for Windows.

## Results

### The diagnostic spectrum

The sample is ordered according to the *diagnostic spectrum* proposed by Angst [33] into four groups: depression, bipolar-II, bipolar-I and mania. By nature, pure mania (M) ($N = 14$) and mania with mild depression (Md) ($N = 16$) were rare, and patients with these conditions had to be merged into one group comprising 30 subjects only. Results are reported in Table 1.

There was a clear difference in the sex ratio across the four groups: women were more common among patients with BP-II (86.7 %) and with major depression (77.6 %), whereas they represented 61.5 % of the group with BP-I and only 50.0 % of the group with mania. Overall, 23.3 % of the patients with mania were still living; they were significantly younger than the other patients, of whom only 10.5 % were alive. The patients with mania and BP-I had an earlier onset of illness than those with MDD and BP-II: in about one quarter before the age of 20. First admissions were lowest in the BP-I group (19.2 %) and highest in the MDD group (56.8 %).

A positive family history of death by suicide was less common among the patients with mania (3.3 %), whereas the other three groups (MDD 19.1 %, BP-II 30.0 % and BP-I 23.1 %) did not differ significantly in this respect. As expected, the patients with mania had by far the lowest suicide rate (3.3 %), whereas 15.05 % of the patients with major depression had died by suicide. It is remarkable that only one further suicide had occurred (n.s.) since the previous follow-up 6 years earlier. Over their lifetimes, 41.0 % of patients with depression, 45.0 % of patients with BP-II, 37.7 % of patients with BP-I but only 10.9 % of manic patients had attempted suicide.

The opposite is true with regard to psychotic symptoms, which were observed in 66.7 % of patients with mania and in 61.5 % of patients with BP-I as compared to 23.3 % of patients with BP-II and 26.3 % of depressed patients.

There were no great overall differences regarding comorbid substance use disorders, but alcohol use disorders were clearly more frequent among the patients with mania and with BP-I, while abuse of sedatives and analgesics was more common in the patients with depression and those with BP-II. With respect to socio-demographic data, there were only minor differences between the four groups.

For descriptive purposes, we also listed the frequency of treatment and duration of long-term medication given to the four groups. The two bipolar patient groups were clearly more often treated for longer periods (BP-I 66.9 % and BP-II 53.3 %) than the patients with unipolar depression (37.2 %) and with mania (33.3 %).

The six personality types showed interesting distributions across the mood spectrum. As expected, the melancholic, the anxious, insecure and the unrealistic, dreamy types were most frequent among patients with MDD, whereas the three other types (relaxed, easy-going; manic; nervous, tense) were most pronounced among patients with mania.

### Unipolar and bipolar patients: living versus deceased

A comparison of the 46 patients still living with the 357 who had died revealed no significant differences with regard to school education, broken home, psychotic features or substance use disorders (Table 2). However, there were significant differences in their personality types: fewer anxious, insecure patients with unipolar depression had died, and, among patients with BP, those still living were more frequently of the manic and the relaxed, easy-going personality types. Generally, among the patients still living, whether unipolar or bipolar, the unrealistic, dreamy personality type was more common.

**Table 1** Characteristics of diagnostic subgroups in 2009

| | D (MDD) (1) | Dm (BP-II) (2) | MD (BP-I) (3) | M(d) (Mania[a]) (4) | *p* (1–4) |
|---|---|---|---|---|---|
| Subjects (*N*) | 183 | 60 | 130 | 30 | |
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | |
| Males | 41 | 8 | 50 | 15 | .0001 |
| Female | 142 (77.6) | 52 (86.7) | 80 (61.5) | 15 (50.0) | |
| Family history of suicides | 35 (19.1) | 18 (30.0) | 30 (23.1) | 1 (3.3) | .03 |
| Education | | | | | |
| Special schooling | 14 (7.6) | 9 (15.0) | 25 (19.4) | 1 (3.3) | .002 |
| Primary/secondary school | 161 (88.9) | 48 (80.0) | 89 (69.0) | 27 (90.0) | |
| Higher education | 8 (4.4) | 3 (5.0) | 15 (11.6) | 2 (6.7) | |
| | Median (Q1–Q3) | Median (Q1–Q3) | Median (Q1–Q3) | Median (Q1–Q3) | |
| Age at onset | 46 (31–57) | 37 (26–47) | 26 (21–39) | 28 (20–37) | .0000 |
| Age at follow-up/death | 77 (67–83) | 79 (72.5–86) | 74.5 (65–80) | 74.5 (65–77) | .001 |
| Personality type | | | | | |
| Melancholic type | 56 (44–64) | 50 (33–60) | 28 (17–50) | 20 (17–35) | .0000 |
| Relaxed, easy-going type | 36 (35–50) | 38 (28–44) | 30 (26–50) | 42.5 (21–52) | .09 |
| Manic type | 19 (14–25) | 21 (13–31) | 19 (13–36) | 32 (17–48) | .02 |
| Nervous, tense type | 16 (12–20) | 17(13–25) | 17(12–28) | 23.5(13–41) | .12 |
| Unrealistic, dreamy type | 30 (21–39) | 27 (19–37) | 20 (13–32) | 17 (10–24) | .0000 |
| Anxious, insecure type | 33 (25–39) | 27 (20–35) | 22 (15–31) | 18 (12–22) | .0000 |
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | |
| First admissions | 104 (56.8) | 22 (36.7) | 25 (19.2) | 12(40.0) | .0001 |
| Psychotic features | 26.3 | 23.3 | 61.5 | 66.7 | .0001 |
| Suicide attempts | 41.0 | 45.0 | 37.7 | 10.0 | .008 |
| Substance use disorders (SUD) | 10.2 | 11.7 | 16.9 | 10.0 | .34 |
| Alcohol use disorders | 5.5 | 3.3 | 14.6 | 10.0 | .02 |
| Sedatives, analgesics | 4.9 | 11.7 | 3.1 | 0 | .04 |
| Long-term medication (≥6 months) | | | | | |
| Lithium | 6.3 | 23.3 | 42.3 | 23.3 | .0001 |
| Neuroleptics | 29.5 | 36.4 | 63.9 | 33.3 | .0001 |
| Antidepressants | 33.9 | 50.0 | 50.6 | 9.1 | .0005 |
| No long-term medication | 62.8 | 46.7 | 33.1 | 66.7 | .0001 |
| Any long-term medication | 37.2 | 53.3 | 66.9 | 33.3 | |
| | Mean (s) | Mean (s) | Mean (s) | Mean (s) | |
| Long-term medication (years) | | | | | |
| Lithium | 7.5 (2.4) | 4.7 (4.4) | 8.2 (6.4) | 6.5 (3.8) | .23 |
| Neuroleptics | 4.8 (5.0) | 7.6 (7.3) | 7.3 (5.4) | 3.2 (3.9) | .004 |
| Antidepressants | 5.1 (4.8) | 7.0 (4.6) | 3.3 (3.0) | 0.0 | .001 |
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | |
| Mortality (2009) | | | | | |
| Deceased ($N = 352$) | 165 (90.2) | 53 (88.3) | 116 (89.2) | 23 (76.7) | .20 |
| Living ($N = 46$) | 18 (9.8) | 7 (11.7) | 14 (10.8) | 7 (23.3) | |
| Deaths by suicide ($N = 46$) | 28 (15.3) | 4 (6.7) | 13 (10.0) | 1 (3.33) | .10 |

[a] Including mania with mild depression

**Table 2** Characteristics of unipolar and bipolar patients, living versus deceased

| | Unipolar | | | Bipolar | | |
|---|---|---|---|---|---|---|
| | Alive | Dead | *p* | Alive | Dead | *p* |
| *N** | 18 | 165 | | 28 | 192 | |
| | *N* (%) | *N* (%) | | *N* (%) | *N* (%) | |
| School education | | | | | | |
| Special schooling | 0 | 8 (4.8) | .26 | 4 (14.3) | 16 (8.4) | .12 |
| Primary/secondary school | 18 (100) | 143 (86.7) | | 23 (82.1) | 141 (73.8) | |
| Higher education | 0 | 14 (8.5) | | 1 (3.6) | 34 (17.8) | |
| Broken home | | | | | | |
| Yes | 6 (33.3) | 58 (35.2) | .88 | 4 (14–3) | 34 (17.7) | .66 |
| No | 12 | 107 | | 24 | 158 | |
| Psychotic | | | | | | |
| Yes | 14 (77.8) | 121 (73.3) | .69 | 12 (42.9) | 94 (49.0) | .55 |
| No | 4 (19.0) | 44 (26.7) | | 16 (57.1) | 98 (51.0) | |
| Substance use disorders | | | | | | |
| Yes | 0 | 19 (11.5) | .13 | 3 (10.7) | 29 (15.1) | .54 |
| No | 18 (100) | 146 (88.5) | | 25 (8.3) | 163 (84.9) | |
| | Median (Q1–Q3) | Median (Q1–Q3) | | Median (Q1–Q3) | Median (Q1–Q3) | |
| Personality type | | | | | | |
| Melancholic type | 57.5 (56–64) | 55 (43.64) | .12 | 46 (19–57) | 33 (19–52) | .30 |
| Relaxed, easy-going type | 34.5 (28–41) | 36 (28–45) | .72 | 46 (33–53) | 32 (18–47) | .006 |
| Manic type | 18 (15–19) | 19 (14–25) | .42 | 27 (18–48) | 20 (12–35) | .02 |
| Nervous, tense type | 16.5 (12–20) | 16 (12–20) | .81 | 20 (15–43) | 17 (12–28) | .08 |
| Unrealistic, dreamy type | 41 (76–48) | 28 (21–36) | .0000 | 31 (18–38) | 21 (13–32) | .05 |
| Anxious, insecure type | 43.5 (38–42) | 29 (20–37) | .0000 | 26 (18–34) | 23 (15–32) | .17 |

* See Table 3 for SMR

## Causes of death

A total of 357 (88.6 %) of the 403 patients had died. With the exception of the BP-II group (with the highest proportion of women), the other three groups of patients with mood disorders had a significant elevation in overall mortality (SMRs): MDD (1.57), BP-I (1.86), M(d) 1.93 as shown in Table 3 on causes of death. Two findings are of particular interest: first, the systematic increase in *cardiovascular mortality* from MDD via the bipolar subgroups to mania. The risk of cardiovascular death among patients with MDD was only slightly higher (SMR = 1.32, n.s.), twofold higher among patients with BP-I disorder (SMR 1.99), but threefold higher among patients with mania (SMR 3.17). Second, deaths by *suicide* were most elevated among patients with MDD (SMR 23.6) and with BP-I (SMR 12.0); in the other two patient groups, the SMRs were less elevated and not significant probably owing to the smaller number of cases. The survival curves demonstrate the early occurrence of suicides in the course of the illness. Only among patients with MDD did suicide persist as a cause of death into old age: in the previous 12 years, two depressed patients but not a single patient with bipolar disorder or mania had died by suicide (Fig. 1).

## Survival analysis

### *Simple regression of patients with MDD and BP*

In simple analyses, the statistically significant predictors of increased all-cause mortality varied to a certain extent between unipolar depressed and bipolar patients.

In *patients with UP* predictors were higher age at first episode, higher proportion of total observation time spent in illness, lower GAS score during the interval between episodes, personality type (low anxious, insecure; low unrealistic, dreamy; high nervous, tense), repeated as opposed to first hospitalisation, lack of long-term medication and low psychotic symptoms. *In patients with BP* the predictors were higher age at first episode, higher

proportion of total observation time spent in illness, lower GAS score during the interval, personality type (low unrealistic, dreamy; low relaxed, easy-going), male sex, repeated as opposed to first hospitalisations, lack of long-term medication, low psychotic symptoms, low level of education and positive family history of suicide.

**Table 3** Mood disorder subtypes and causes of death

| Cause of death | D (MDD) | Dm (BP-II) | MD (BP-I) | M(d) (mania) |
|---|---|---|---|---|
| Deaths (*N*) | 161 | 53 | 116 | 23 |
| % | | | | |
| Neoplasm | 15.8 | 7.6 | 17.2 | 8.7 |
| Cardiovascular disease | 27.9 | 50.9 | 33.6 | 47.8 |
| Cerebrovascular disease | 9.7 | 7.6 | 5.2 | 8.7 |
| Accident | 4.2 | 1.9 | 5.2 | 4.4 |
| Suicide | 17.0 | 7.6 | 11.2 | 4.4 |
| Other | 23.0 | 17.0 | 24.1 | 13.0 |
| SMR | | | | |
| Neoplasm | 1.08 | 0.40(*) | 1.20 | 0.61 |
| Cardiovascular disease | 1.32 | 1.60(*) | 1.99** | 3.17* |
| Cerebrovascular disease | 0.95 | 0.52 | 0.73 | 1.37 |
| Accident | 1.74 | 0.54 | 2.36 | 1.99 |
| Suicide | 23.57*** | 9.88 | 12.02** | 4.32 |
| Other | 1.50* | 0.74 | 1.89* | 0.97 |
| Total | 1.57*** | 1.10 | 1.86*** | 1.93* |

* $p < .05$, ** $p < .01$, *** $p < .001$, (*) $p < .1$, compared to Swiss population

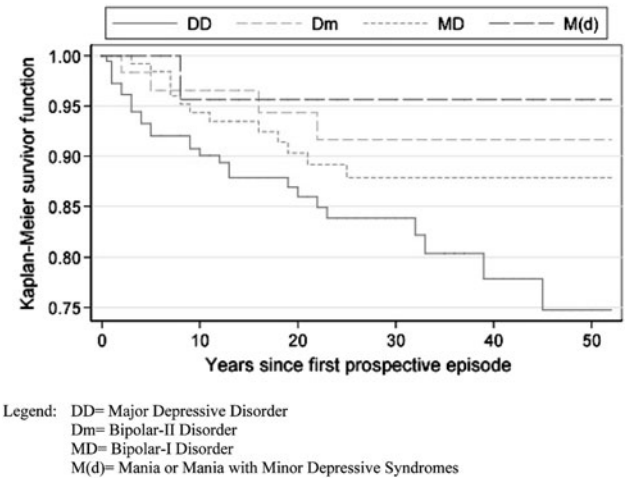


**Fig. 1** Survivorship of suicide by diagnosis in 403 patients with mood disorder. *DD* major depressive disorder, *Dm* bipolar-II disorder, *MD* bipolar-I disorder, *M(d)* mania or mania with minor depressive syndromes

Substantial covariance was found between the unrealistic, dreamy and the anxious, insecure personality types, and between the GAS score during the interval and the proportion of total observation time spent in illness. To avoid multi-collinearity in the multiple analysis, we retained only the stronger bivariate predictor of the inter-related pairs, that is, anxious, insecure personality type and the proportion of total observation time spent in illness in patients with UP, and the GAS interval score in patients with BP. The assumption of proportional hazards was not violated for the anxious, insecure, the unrealistic, dreamy, and the relaxed, easy-going personality types, for educational level and for the GAS score during interval. All other predictors were time-dependent.

### *Multiple regression of patients with MDD*

Risk factors of mortality in patients with UP are shown in Table 4. The anxious, insecure personality type yielded a weak effect, a standard deviation increase reduced the mortality risk by 20.6 % (HR = 0.829). The nervous, tense type markedly increased the hazard ratio (HR = 4.134; 313.4 %), but the effect was observed only during years 40–52 after entry into the study. The hazard ratio represented by the proportion of time ill was slightly increased

**Table 4** Final model for multiple risk factors of mortality in patients with unipolar depression

| Predictors | Hazard ratio (HR) | 95 % CI | Sig. |
|---|---|---|---|
| Anxious, insecure type[a] | 0.829 | 0.690–0.997 | 0.047 |
| Nervous, tense type[a] | | | |
| 40–52 years | 4.134 | 1.046–16.340 | 0.043 |
| Proportion of time ill[a] | | | |
| 1–9 years | 1.512 | 1.248–1.832 | 0.000 |
| Long-term medication | | | |
| 1–9 years | 0.296 | 0.128–0.682 | 0.004 |
| Age at first episode[a] | | | |
| 1–9 years | 1.406 | 1.017–1.943 | 0.039 |
| 10–19 years | 2.821 | 1.935–4.114 | 0.000 |
| 20–29 years | 2.117 | 1.349–3.321 | 0.001 |
| 30–39 years | 1.862 | 1.098–3.159 | 0.021 |
| 40–52 years | 3.428 | 1.449–8.107 | 0.005 |
| Psychotic symptoms | | | |
| 1–9 years | 0.198 | 0.047–0.826 | 0.026 |
| Repeated hospitalisations | | | |
| 20–29 years | 2.061 | 0.995–4.270 | 0.052 |
| 30–39 years | 3.469 | 1.540–7.814 | 0.003 |

Time-dependent predictors are divided into separate intervals. Time refers to years after study entry

[a] Standardised continuous measure: The HR refers to 1 standard deviation increase in the respective scale

during the first 9 years (HR = 1.512). Long-term medication reduced the mortality risk more than threefold during the first 9 years (HR = 0.296) but yielded no significant associations thereafter. A higher age at first episode significantly increased the mortality risk throughout the 52 years of the study (HR = 1.406–3.428). As expected, the hazard ratio was highest during the last interval from years 40–52 (HR = 3.428). Conversely, psychotic symptoms during the first 9 years reduced the hazard ratio (HR = 0.198). If the patient's admission at study entry was a readmission, mortality risk was increased during years 20–29 (HR = 2.061) and 30–39 (HR = 3.469).

*Multiple regression of patients with BP*

Different predictors were found with respect to patients with BP (see Table 5). A relaxed, easy-going personality lowered the mortality risk by 31.6 % (HR = 0.760.). A standard deviation increase in the GAS interval score reduced the mortality risk by 64.7 % (HR = 0.607). Long-term medication considerably reduced the mortality risk during the first 19 years of the study (HR = 0.072–0.312) and being female reduced it from years 20–39 (HR = 0.233–0.372). Except during the first 9 years, a higher age at first episode was again significantly associated with an increased hazard ratio throughout the observation period (HR = 1.814–3.369). Having a higher education reduced the mortality risk over the whole period of observation by 55.5 % (HR = 0.643). Psychotic symptoms reduced the mortality risk from years 10–29 (HR = 0.195–0.511). Finally, we found that, among patients with BP (unlike those with UP), the mortality risk increased in association with deaths by suicide in relatives for the years 30–39 (HR = 3.215) and 40–52 (HR = 4.994).

**Table 5** Final model for multiple risk factors of mortality in patients with bipolar disorder

| Predictors | Hazard ratio (HR) | 95 % CI | Sig. |
|---|---|---|---|
| Relaxed, easy-going type[a] | 0.760 | 0.625–0.925 | 0.006 |
| GAS interval score[a] | 0.607 | 0.492–0.749 | 0.000 |
| Long-term medication | | | |
| 1–9 years | 0.072 | 0.009–0.600 | 0.015 |
| 10–19 years | 0.312 | 0.095–1.024 | 0.055 |
| Female gender | | | |
| 20–29 years | 0.233 | 0.117–0.465 | 0.000 |
| 30–39 years | 0.372 | 0.122–1.134 | 0.082 |
| Age at first episode[a] | | | |
| 10–19 years | 1.814 | 1.012–3.252 | 0.045 |
| 20–29 years | 2.757 | 1.783–4.262 | 0.000 |
| 30–39 years | 3.197 | 1.773–5.766 | 0.000 |
| 40–52 years | 3.369 | 1.425–7.965 | 0.006 |
| Psychotic symptoms | | | |
| 10–19 years | 0.195 | 0.040–0.941 | 0.042 |
| 20–29 years | 0.511 | 0.263–0.993 | 0.048 |
| Higher education | 0.643 | 0.429–0.963 | 0.032 |
| Suicide history in relatives | | | |
| 30–39 years | 3.215 | 1.379–7.492 | 0.007 |
| 40–52 years | 4.994 | 1.735–14.372 | 0.003 |

Time-dependent predictors are divided into separate intervals. Time refers to years after study entry

[a] Standardised continuous measure: The HR refers to 1 standard deviation increase in the respective scale

## Discussion

This study on mortality has several strengths: it covers a broad spectrum of patients with different subgroups of mood disorders, it is a prospective study conducted over decades until 90 % of the patients had died, and it includes a number of personality characteristics.

Unsurprisingly, we found the overall mortality among patients with severe mood disorders to be elevated, which is in agreement with most of the literature mentioned in the introduction. But in addition, our data demonstrate in particular the practical relevance of distinguishing between subgroups of mood disorders (MDD, BP-II, BP-I, mania). An exception to these elevated mortality rates was patients with BP-II disorders ($N = 53$) with an overall SMR of 1.10 (n.s.). This group had the highest rate of women (86.7 %). Only 8 patients were males, which is of course a severe limitation of the findings. BP-II patients manifested a trend ($p < .10$) to lower mortality by neoplasm (SMR 0.40) and a slightly elevated risk for cardiovascular disease (SMR 1.60).

Deaths by *suicide* were systematically associated with the depressive component of the diagnostic spectrum. They were 4–23-fold more common than in the normal population and about twice as frequent among patients with MDD (SMR 23.1) than among those with BP-I disorder (SMR 12.0). Suicides among patients with BP-II (SMR 9.9) and mania (SMR 4.3) were also considerably elevated but the findings did not reach significance, apparently owing to the small number of cases.

The reverse was found for *cardiovascular deaths*, which increased systematically with the manic component. While patients with MDD (SMR 1.32) did not differ significantly from controls and patients with BP-II showed a trend to an elevation (SMR 1.6, $p < .10$), patients with BP-I had double and patients with mania triple the risk of dying from a cardiovascular disorder (SMR 3.17) not yet reported in the literature.

The other findings are in line with recent papers. Fiedorowicz et al. [34] found patients with BP-I had more than double the risk of dying from a cardiovascular disorder than those with BP-II, compatible with the papers of Garcia-Portilla et al. [35], and the reviews of Weiner et al. [18] and Munk Laursen et al. [16].

On the other hand, there is an ongoing debate about the elevation and causation of cardiovascular mortality among depressed patients. Depression following myocardial infarction was found to be clearly associated with higher mortality [36]; a bidirectional relationship between cardiovascular disease and depression was stressed in the review of Baune et al. [37]; a high level of methodological heterogeneity was found in the review of van der Kooy et al. [38] and a meta-analysis of 54 studies found uncertainty as to whether depression is an independent risk factor for coronary heart disease [39]. Our unclear result regarding higher mortality among depressed patients is in accord with this uncertainty.

The increased cardiovascular deaths in patients with mania may be due to factors of lifestyle (such as nutrition and alcohol consumption) in contrast to the more cautious lifestyle of patients with an anxious, insecure personality type, more prominent in patients with MDD. An association between psychological distress and cardiovascular mortality was recently found in meta-analyses of 10 prospective cohort studies from England [40]. The associations between mortality and a positive family history of deaths by suicide and a severe course of the illness expressed by the percentage of time spent in episodes during the follow-up period are unsurprising. It is important to note that a later age at onset is related to an increased mortality in both the UP and BP patient groups; late-onset affective disorder thus requires special attention and the prescription of long-term medication; the latter was found to be effective in lowering mortality in this study.

Of special interest are the associations between *personality types* and mortality: having a nervous, tense personality type increased mortality among depressed patients. A similar relationship with suicide attempts was found earlier in a large prospective study of young men tested at age 19 and followed up to the age of 31 [41]. This is compatible with the literature on aggression or impulsivity [42, 43] and suicidality [44, 45].

An unexpected finding was the protective effect of being anxious and insecure in patients with MDD. Intuitively, this makes sense, but we were unable to associate this effect with any specific cause of death; for instance, we did not find that anxious, insecure patients had a lower accident or suicide rate. So we hypothesise that this personality type is associated with a more cautious lifestyle in general.

Patients with bipolar disorder had very different predictors of mortality: mortality was reduced by a higher education (an effect of lifestyle?) and increased by a family history of death by suicide (significantly more common in the BP than in the UP patient group). This finding is in agreement with recent papers [44, 46, 47]. A better inter-episode remission lowered the mortality rate, as did long-term medication. A relaxed, easy-going personality type was also linked with lower mortality and may be an indicator of a lower stress sensitivity. The associations of personality types with subtypes of affective disorders as indicated in Table 1 are in almost perfect agreement with von Zerssen's original concept of such relationships [48].

Of interest are the differences between patients with mania and those with BP-I disorders. Overall, the mortality was very high in both groups (SMR 1.93 vs. 1.86), although there were marked differences in their respective rates of suicide attempts (10 vs. 37.7 %) and suicides (4.4 vs. 11.2 %), the latter illustrated also by the SMRs (4.32 vs. 12.02). Compatible with these findings is the much lower family history for suicides among patients with mania (3.3 %) than patients with BP-I disorders (23.1 %). Finally, manic patients tended to score higher on the manic type and relaxed, easy-going type of personality than did patients with BP-I disorder. In this context, the results of the NCS-A study of 10,123 adolescents, which point to a considerable lifetime prevalence of mania alone (1.7 %) are relevant [49]. These findings cannot prove mania to be an independent disorder but they do suggest that it should be distinguished from BP-I disorder for the purpose of further research.

This study has the following *limitations*: all patients had been admitted to a psychiatric hospital and represent only the most severe subgroup of persons suffering from mood disorders in the general population. The clinical follow-up lasted 25 years and ended in 1985; after that, only mortality data were available. The treatment received after 1985 is unknown. The number of patients with mania ($N = 30$) or BP-II ($N = 60$) was comparatively small, which may have led to type II errors in the comparison of SMRs. We did not correct the $\alpha$ level in multiple survival analyses because the effect sizes achieved were high and the probability of type I errors thus low. However, because of the small $N$ in some analyses, a correction of the $\alpha$ level would have increased the type II error markedly. Post hoc power analyses revealed that an $\alpha$ correction would have reduced our statistical power ($1 - \beta$) to an non-acceptable degree of 0.5 or lower, whereas without correction, it was 0.8 or higher.

## Conclusions

There is a need for prospective studies of mood disorder patients which follow them to the end of their lives. The

differences in the causes of death across the mood spectrum from depression via bipolar subgroups to mania confirm the validity of the distinction between the diagnostic groups.

**Conflict of interest** The authors declare that they have no conflict of interest.

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